REMARKS

Interview of April 20, 2004

Applicants acknowledge with appreciation the interview between Examiner Parkin, Examiner Housel, Dr. Fehlner, J. Chumney, and Dr. Kendall Smith.

Status of the Claims

Claims 1, 9, 15 and 16 have been amended. Support for the amendment to claim 1 can be found on page 14, lines 27-28 and page 15, lines 14-16 of the application. Support for the amendment to claim 9 can be found in the claims as originally filed, and on page 16, line 28 to page 17, line 3 of the application. Claims 15 and 16 have been amended to depend from newly added claim 18.

Claims 17-26 have been added. Support for claims 17 and 24 can be found on page 20, lines 26-29 of the application. Applicant notes that doses up to 1,500,000 IU IL-2/m^2 body surface/day are in view of formulations requiring relatively higher dosages to provide a given amount of bioavailable IL-2, e.g. Chiron IL-2 (see page 20, lines 21-23 of the application). These dosages do not elicit toxicity of Grade 1 or higher as defined by the World Health Organization. Support for claims 18-21, 23, and 25-26 can be found in the claims as originally filed. Support for claim 22 can be found on page 13, lines 7-10 of the application.

Claims 2-4, 9, and 11-14, have been canceled without prejudice or disclaimer. Accordingly, claims 1, 5-8, 10, and 15-26 are pending and at issue.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-12, 15 and 16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Regarding claim 1, the Examiner alleges that the term "potentiation" has an art-recognized meaning, referring to a pharmacological interaction between two or more agents/drugs that results

in a pharmacologic response that is greater than the sum of individual responses to each drug or agent. According to the Examiner, the methodology of the present invention only describes the administration of a single agent (IL-2), and does not disclose the administration of another agent or describe the various effects that are potentiated by IL-2 and the other agent.

Applicants respectfully note that the term "immune potentiation" is defined on page 14, lines 27 - 28 as the "enhancement of the ability of the immune system to mount an effective immune response". Consistent with the originally intended meaning and scope of the claim, claim 1 has been amended to recite "A method for enhancing the ability of the immune system to mount an efffective immune response . . ." Applicants respectfully request that the rejection be withdrawn.

The Examiner also objects to the phrase "an amount [of a composition comprising IL-2] effective to maintain immune ehancement" as vague and indefinite since, according to the Examiner, the precise immunological properties affected are not disclosed. Applicants note that on page 15, lines 14-16 of the present application "immune enhancement is defined by a normal concentration of circulating CD4 + T cells with elevated CD8 + T cells and elevated Natural Killer (NK) cells beyond the normal range". See also page 32, lines 14-17, and page 34, lines 5-8 of the application. Consistent with the originally intended meaning and scope of the claim, claim 1 has been amended to recite "an amount effective to maintain at least a normal concentration of circulating CD4+ T cells and an elevated concentration of CD8 + T cells and Natural Killer cells . . ." Applicants respectfully request that the rejection be withdrawn.

Regarding claim 9, the examiner alleges that the term "immune reconstituted" is vague and indefinite since the precise genotype/phenotype is not readily manifest. Applicants have amended claim 9 to refer to a subject who "has undergone treatment for an immunodeficiency condition and the subject is administered IL-2 prior to vaccination". Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-4, 8-10, 15 and 16 stand rejected under 35 U.S.C. §103(a) as obvious over Lane (U.S. Pat. No. 6,190,656) in view of Vandamme et al. The Examiner states that Lane teaches the *concomitant* administration of both IL-2 and an antiviral agent to HIV-1 infected patients, and Vandamme discloses that patient compliance while on antiretrovirals is problematic.

The Examiner admits that Lane does not address the timing of IL-2 administration with respect to the discontinuation of viral therapy or prior to a vaccination regimen.

Nevertheless, the Examiner alleges that a person of ordinary skill "would have been motivated to administer low-dose IL-2 therapy to virally-infected patients since this would provide a useful means for activating and restoring immune function in patients who can no longer tolerate antiretroviral therapy." Moreover, according to the Examiner, antiretrovirals are not directed toward the immune system and many virally infected patients suffer from immune dysfunction.

Applicant respectfully notes that neither Lane nor Vandamme teach or suggest a method for the enhancement of the ability of the immune system to mount an effective immune response to an infectious disease after the discontinuation of treatment for the infection or prior to vaccination. The Examiner admits that this limitation is missing from Lane. Vandamme merely teaches a dosage regimen for combating resistance to antiviral therapy, and does not teach or suggest the administration of IL-2. Accordingly, the combined references fail to teach or suggest a method for the enhancement of the ability of the immune system to mount an effective response to an infectious disease after the discontinuation of treatment for the infection or prior to vaccination.

Moreover, the cited references teach away from administering IL-2 after the discontinuation of treatment for the infection. The Examiner relies upon the Examples of Lane, which "employed the concomitant administration of both IL-2 and an antiviral agent to HIV-1 infected patients." The Examples in Lane, however, are premised on the widely-held belief that:

> **Because of concerns that IL-2 could lead to enhanced HIV replication,** anti-retroviral therapy.... was administered throughout the study (Lane, col. 20, lines 45-47, emphasis added).

Given such concerns, a person of ordinary skill in the art would not be motivated to administer IL-2 after the discontinuation of treatment for the infection. To the contrary, a person of ordinary skill based on Lane, would be motivated to not administer IL-2 after the discontinuation of treatment for the infection, since IL-2 is thought to possibly lead to enhanced HIV replication. In the face of such concerns, embodiments of the present invention expressly teach administering IL-2 after the *discontinuation* of antiviral treatment, which represents an unobvious advancement over prior art, such as Lane, which teach against such a technique.

Claims 5-7, 11, and 12 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Tilg et al. in view of Tsai and Huang. The Examiner states that Tilg teaches the administration of low-dose IL-2 therapy to HBV-infected patients who are not undergoing antiviral therapeutic regimens, and Tsai and Huang report that both HBV and HCV-infected patients utilize similar immune mechanisms to remain in asymptomatic states. The Examiner alleges that it would have been prima facie obvious to one having ordinary skill in the art to administer low-dose IL-2 therapy as taught by Tilg, to HCV-infected patients. Further, according to the Examiner, a skilled artisan would also have been motivated to include a known antiviral in the therapeutic regimen as well.

Applicants note that independent claim 11, and dependent claim 12 have been canceled without prejudice or disclaimer. With respect to claims 5-7, neither Tilg nor Tsai and Huang teach or suggest limitations of claim 1. For example, Tilg and Tsai and Huang do not teach or suggest a method for enhancing the ability of the immune system to mount an effective immune response after the discontinuation of treatment for an infectious disease or to vaccination. Applicants respectfully request that the rejection be withdrawn.

Non-statutory Double Patenting Rejection

Claims 1-12, 15 and 16 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-57 of U.S. Patent No. 6,509,313 in view of Vandamme. Claims 1-12, 15 and 16 also stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-60 of U.S. Patent No. 6,045,788 in view of Vandamme. The '313 Patent is a continuation-in-part of the '788 Patent.

The '313 and '788 Patents teach and recite the administration of anti-viral agents along with IL-2, i.e at the same time (See '313 Patent, lines 57-66). The Examiner admits that the '313 and '788 Patents, like Lane (discussed above), do not discuss the timing of administration of low-dose IL-2 in reference to anti-viral therapies. Vandamme merely teaches drug combinations to combat resistance in anti-viral therapy regimens.

As discussed above, Vandamme does not teach the administration of IL-2, and attempts to cope with the long-term effects of drug resistance by changing anti-viral drug regimens. Vandamme does not teach providing an alternative approach to the problems of long-term treatment of an infectious disease, for example, HAART. On the other hand, Applicant discloses a novel approach, i.e. *discontinuing* treatment for the infectious disease and administering IL-2. Thus, the cited references do not teach or suggest a method for enhancing the ability of the immune system to mount an effective immune response after the discontinuation of treatment for an infectious disease.

Furthermore, administering IL-2 after the discontinuation of treatment for an infectious disease, such as HIV, is not obvious over administering IL-2 along with, for example, HAART. Conventional thinking, embodied in Lane discussed above, addresses perceived concerns of IL-2 leading to enhanced HIV replication. The '313 and '788 Patents teach concomitant administration of IL-2. The '313 and '788 Patents do not teach *discontinuing* IL-2 treatment, and administering IL-2, as such a method would directly conflict with the previously held view that IL-2 may lead to enhanced HIV replication. Applicant respectfully submits that that methodology explicitly calling for administration of

IL-2 after discontinuing IL-2 treatment represents an unobvious contribution to the state of the art.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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